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EFFECT OF PROLONGED ADMINISTRATION OF IODINE CONTAINING  
WATER PURIFICATION TABLETS IN MAN

FINAL REPORT

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13. ABSTRACT (Maximum 200 words)  <p>Tetraglycine hydroperiodide tablets purify water by liberating 8 milligrams of iodine per tablet. The effects on thyroid size, function, and iodine uptake resulting from ingestion of four of these tablets daily for three months were studied in eight healthy volunteers. Thyroid size was determined by ultrasound. The thyroid-pituitary axis was assessed by bolus thyrotropin releasing hormone (TRH) tests. Urinary iodide levels increased from 0.276 to 40 mg/d. The mean RAIU fell and remained less than 2%. As thyroxine levels declined, basal thyroid stimulating hormone (TSH) and TSH response to TRH rose. In all subjects, thyroid volume increased. No clinical signs of either hyperthyroidism or hypothyroidism occurred. We conclude that in response to a sustained increment in TSH, the normal thyroid enlarges to adapt to the iodine from continuous use of tetraglycine hydroperiodide water purification tablets.</p>				
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Tetraglycine Hydroperiodide (TGH) tablets are used by outdoors enthusiasts and the American military to purify potentially contaminated water sources, and release approximately 8 milligrams of elemental iodine per tablet. They are available over the counter, and are stockpiled by the American military to be used in field situations for varying lengths of time. Iodine, in a variety of formulations, affects thyroid function (1-8). This particular iodide has not been studied and may be used by a variety of people for potentially prolonged periods. We investigated the effects of ingesting four TGH tablets daily on thyrotropin (TSH), thyroid hormone levels, thyroid volume by ultrasound, and 24-hour radioactive iodine uptake in healthy volunteers.

### Subjects and Methods

Eight healthy, euthyroid volunteers comprised of six men and two women, completed the study. None had a history of thyroid disease, other chronic medical disorder or took medications containing iodine or with known effect on thyroid function. No subject had a history of adverse reaction to iodine containing preparations. All signed informed consent before entering the study. The protocol and consent were reviewed and approved by the Fitzsimons Army Medical Center Institutional Review Committee. United States Army quartermaster supply provided the Tetraglycine Hydroperiodide water purification tablets. Baseline twenty-four hour  $^{131}\text{I}$  iodine uptake ( $24^\circ$  RAIU), thyroxine (T-4), triiodothyronine (T-3), thyrotropin (TSH), TSH response to thyrotropin releasing hormone (TSH20), thyroid volume by ultrasound, serum iodine and twenty-four hour urinary iodine excretion were performed on each volunteer. Subjects were then instructed to take four water purification tablets per day dissolved in water or juice for ninety days.  $24^\circ$  RAIU was repeated at days 7 and 28, T-4, T-3, TSH and TSH20 at days 7, 28, and 90; ultrasonic thyroid volume at days 35 and 90; and serum and urinary iodines at days 7, 28, and 90.

Twenty-four hour RAIU was performed in the standard fashion, but using one microcurie of  $^{131}\text{I}$  and longer counting times. T-4 measurement was by T4 Plus TDX system (Abbott Diagnostics, Inc., North Chicago, Illinois). This Fluorescent Polarization immunoassay method has a specific intraassay coefficient of variation (CV) of 4.5%. Serum T-3 was measured by radioimmunoassay (Autopack T-3 RIA Kit, Horsham, Pennsylvania) with an intraassay CV of 4.7%. TSH20 was performed by drawing blood for serum TSH before and twenty minutes after intravenous injection of 500 micrograms of thyrotropin releasing hormone (Thypinone, Abbott, North Chicago, Illinois). TSH was measured by IMx Ultrasensitive hTSH Assay based on the microparticle enzyme immunoassay (MEIA) technology (Abbott Laboratories Abbott Park, Illinois) with an intraassay CV of 3.3-5.2%.

Thyroid volume was determined by ultrasound as described by Rasmussen (9) using a Picker Echoview system model 80L, Echoview system 80C ultrasound machine with a Rohe 7.5 megahertz/6mm 2 OM focus transducer. Briefly, longitudinal images were recorded to determine right and left lobe lengths. Serial transverse images were then made through each lobe at one half to one centimeter intervals based on length. Images were recorded on radiographic film and traced for digitization and volume calculation utilizing Sigma Scan and Sigma Plot computer software programs.

Serum and urine iodines were performed by autoanalyzer utilizing ion exchange and catalytic reduction methods (S.K. Bioscience Labs, 6330 Variel Ave., Woodland Hills, California). Serum iodine measurements included protein bound, inorganic, and total iodine.

Data was analyzed for statistical significance by ANOVA and Student Newman Kewls.

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### Results

The results are summarized in table 1 as group means with standard errors. RAIU was virtually completely suppressed at day 7 and remained so on day 28. The mean T-4 fell slightly but not significantly on day 7 compared to baseline, and stayed slightly below the pre-treatment value on days 28 and 90. Mean T-3 was also lower than the initial value on day 7, but rose to levels slightly above baseline on days 28 and 90. These changes also failed to reach statistical significance.

Significant and parallel increases were seen in TSH, TSH20, and thyroid volume during the study. The TSH rose and remained significantly above baseline on days 28 and 90. The TSH20 was also significantly higher than baseline on days 7, 28, and on day 90. Thyroid volume increased significantly by day 35, and slightly more by day 90. The increase from day 35 to day 90 was not significant on statistical analysis.

Mean baseline serum and urine iodines were 8.5 ug/dl and 275.7 ug/24° respectively. Serum iodine rose significantly to 104 ug/dl and urine iodine to 37,210 ug/24° on day 7. These values remained elevated on day 28 (serum 140 ug/dl, urine 41,808 ug/24°) and day 90 (serum 153 ug/dl, urine 30,585 ug/24°).

The water purification tablets were well tolerated by all participants. No subject developed signs or symptoms of thyroid dysfunction.

### Discussion

This study shows significant increases in TSH, (TSH20), thyroid volume, a small decrement in T-4, and suppressed 24° RAIU, with intake of 32 mg. of iodine per day in the form of TGH tablets. These changes persisted for the three months of therapy, but were not associated with any clinically evident thyroid dysfunction.

Several studies have shown that healthy volunteers administered 1.5-250 mg of stable iodide per day for shorter durations of up to 2 weeks develop statistically significant decreases in serum levels of thyroid hormones (T4 and T3) and elevated serum thyroid stimulating hormone (TSH) levels (1-7). Administering 30 mg or more as a single dose or 15 mg or more for 12 days also completely suppresses thyroid radio-iodine uptake (4).

Far fewer studies have examined the effects on these variables of more prolonged iodide administration in normal individuals. Euthyroid subjects receiving 72-360 mg per day for 30 days (1) or massive doses of 1080 mg per day for 11 weeks (11) developed persistent alterations of thyroid hormone and TSH levels that were similar in magnitude to those seen in short term studies (1-10) and which appeared to be reversible upon discontinuation of the medication (11).

Three points can be considered from these findings. First, since cold iodine ingestion blocks RAIU, it is recommended as a prophylactic measure to prevent thyroidal accumulation of radioisotopes of iodine in nuclear environments. Potassium iodide has been used for this purpose but may be less readily available to the general public than TGH tablets. TGH tablets, if found to block RAIU with a single dose as well as with prolonged administration, may represent a readily available, convenient and well-tolerated alternative to potassium iodide.

Second, this study shows a significant increase in thyroid volume associated with a mild but significant TSH elevation due to iodine intake. Only one other study has examined the effect of iodine consumption on thyroid volume in normal subjects. Very recently Namba and colleagues reported increases in thyroid volume and thyroglobulin, a slight decline in T-4, and a TSH increase within the normal range in subjects given 27 milligrams of iodine daily for four weeks (8). They speculated the TSH elevation "within the normal range may control thyroid volume and function", and commented that thyroid autoregulation must be reconsidered.

Autoregulation is defined as the "regulation of thyroidal iodine metabolism independent of thyroid-stimulating hormone or other external stimulators" and excess iodine has been considered the major autoregulatory factor (12). This concept is upheld by the observation of highly stable thyroid hormone and TSH levels in iodine sufficient areas with widely varying iodine intake (12). The data from Namba and colleagues and the present study both show an increase in thyroid volume associated with a significant rise in TSH albeit within the normal range. These data support a role for TSH in the human thyroid response to excess iodine.

Third, our subjects, who were all free of known thyroid disease, experienced only subclinical changes in thyroid function within the normal range. However, patients with underlying thyroid disease, such as treated or untreated Graves' disease, Hashimoto's disease, or multinodular goiter, often previously undiagnosed, were much more susceptible to the effect of iodine. When such patients consume large amounts of iodine for prolonged periods, they may develop overt and severe hypothyroidism (13, 14) or paradoxically, and without explanation, thyrotoxicosis (15, 16). Therefore, when administering iodides to large populations, one must be aware that some members are likely to develop significant thyroid dysfunction.

In summary we have shown increases in thyroid volume and TSH, decreased T-4 levels and marked suppression of RAIU by consumption of iodine in the form of tetraglycine hydroperiodide.

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Table 1.

	<u>Baseline</u>	<u>Day 7</u>	<u>Day 28</u>	<u>Day 90</u>
RAIU %	15 ± 2.6	1.2 ± 0.3***	0.7 ± 0.3	NA
T4 ug/dl	6.5 ± 0.2	6.0 ± 0.3	6.0 ± 0.3	6.1 ± 0.3
T3 ng/dl	140 ± 8	128 ± 6	155 ± 10	149 ± 7
TSH uU/ml	1.69 ± 0.09	2.8 ± 0.32*	3.3 ± 0.33*	2.98 ± 0.50*
TSH20 uU/ml	9.9 ± 0.77	14.94 ± 2.41*	18.84 ± 1.72**	16.33 ± 1.69*
	<u>Baseline</u>		<u>Day 35</u>	<u>Day 90</u>
Size (mLs)	14.8 ± 0.9		19.4 ± 1.2 *	20.3 ± 1.4*

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Mean ± SE, \* p< 0.05, \*\*p< 0.01, \*\*\*p< 0.001, ANOVA and SNK